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Clinical Proceedings

OF THE CHILDREN'S HOSPITAL WASHINGTON, D. C.

THALASSEMIA (MEDITERRANEAN ANEMIA).
John A. Papathanasiou, M.D. 137

CYSTIC DISEASE OF THE LUNGS.
George William Ware, M.D. 145

PURPURA IN CHILDHOOD
Jack J. Rheingold, M.D., Sanford Leiken, M.D. 151

EDITORIAL—CHANGE IN STAFF. *George J. Cohen, M.D.* .. 157

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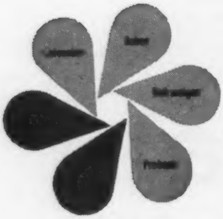

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THALASSEMIA

(MEDITERRANEAN ANEMIA)

John A. Papathanasiou, M.D.*

Thalassemia is an hereditary hemolytic anemia confined largely to persons living on the northern shores of the Mediterranean Sea. The name thalassemia was coined by Whipple and Bradford from the Greek word, *thalassa*, which means sea. Other proposed names include target cell anemia, suggested by Dameshek, and hereditary leptocytosis, recommended since the disease is inherited and leptocytes ("thin cells") are a prominent feature of the disease. These latter two suggested names are not satisfactory since both target cells and leptocytes may be found in the peripheral blood in a variety of diseases.

HISTORICAL REVIEW

In Greece, Aravantinos, in 1920, was the first person to describe this entity as an anemia of unknown etiology. In 1925, Cooley and Lee, in Detroit, systematically studied this disease under the name of "erythroblastic anemia" and separated this anemia from the undetermined and confused group of the pseudoleukemic anemias of children (Jaksch-Hagen-Luget). Cooley emphasized the grave prognosis of erythroblastic anemia, the appearance of the disease in persons of Greek and Italian origin, its hereditary character and skeletal alterations.

Following the original work of Cooley, many reports appeared in American medical literature describing cases of the disease occurring in children of Italian, Greek, Portuguese, Syrian, Armenian, and Spanish origin.

In 1937, Caminopetros, in Athens, published an elaborate and important monograph on the subject, reviewing more than 30 cases. Papers by Chini, et al., indicated a considerable frequency of this condition in Southern Italy and Sicily where a remote Greek ancestry is common. These early reports from Greece and Italy were particularly valuable for the evidence that they presented of the probability of the occurrence of a milder form of the disease in adults and of an hereditary transmission.

In Greece, the anomaly was found in the Peloponnesus and near Athens. Cases were described from the area near Ferrara, Italy, and from Sardinia. Cases were also reported from natives of Cyprus, Malta, Egypt, Algeria and Turkey. Fanconi, in 1935, reported two cases of thalassemia from Switzerland in children of Italo-Dalmatian origin. In 1938, Bywaters reported a case in an English child; in 1943, Rohr a case in a Swiss child who did not appear to have any Italian or Greek blood; Foster (1940) and DeMarsh (1950) cases in Chinese children; Schwartz and Mason (1949) and others, have reported cases in Negroes, and Silvestroni and Bianco (1948) in Egyptians.

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* Resident, Pediatrics.

Thalassemia has been described in Jewish children from Kurdistan, in Iranians, and from inhabitants of the Caspian Sea area. It has been postulated that the pathologic gene may have been brought into Kurdistan by the biblical ancestors of the Jewish Kurds from a large pool of the disease in the Eastern Mediterranean basin.

Recently, large groups of persons with this disease have been reported in Thailand and China. Another investigation showed that a focus of the thalassemia gene exists in India and in the Sikh community in Vancouver, British Columbia, Canada, small numbers of Sikhs having migrated to Vancouver since 1905.

Several reasons for the occurrence of the abnormal gene causing thalassemia in the various countries have been proposed. Mutations may have appeared independently, or different forms of thalassemia may exist in these unrelated groups. A third possibility is based on historical speculation. It is well known that an Aryan migration from Southern Europe into India occurred about 1500 B.C. There is evidence that a similar migration occurred from the Caspian Sea area to China a thousand years earlier. Many centuries later, there were migrations of the Thais from north to south China and finally to Thailand. A large initial reservoir of the abnormal gene causing thalassemia occurring in the Mediterranean basin may have spread to these distant countries.

In 1940, cases of hypochromic anemia in patients of Mediterranean origin, unaccompanied by peripheral erythroblastosis, and characterized by a rather favorable prognosis, but with a clear hereditary character, were described in the American literature. Wintrobe, et al., described such cases as "hereditary hemopoietic disturbance of Italian adolescents and adults" while Dameshek, impressed with the number of target cells in the peripheral blood, termed the condition, "target cell anemia without erythroblasts." These authors were undoubtedly describing the mildest form of thalassemia in which the marked anemia, erythroblastosis and bone lesions are absent. Earlier, in 1925, Rietti, in Ferrara, had described hereditary hypochromic anemia with increased hemolysis, anisocytosis, poikilocytosis and increased resistance to hypotonic saline. Greppi and Micheli extended these observations. It gradually became clear that these first Italian descriptions, as well as the later ones from the United States, all dealt with the same disease, thalassemia minor, or Rietti-Greppi-Micheli disease.

The reluctance to recognize the relationship between Cooley's anemia (thalassemia major) and the milder form (thalassemia minor), in spite of the hereditary character of the latter, and its exclusive appearance in the same people in whom Cooley's anemia appears, must be attributed to the lack of erythroblasts in the peripheral blood in the mild form, such erythroblastosis up to that time having been thought to be a characteristic sign of Mediterranean anemia.

On the basis of these investigations, thalassemia was therefore classified into the following forms:

1) Thalassemia major (Cooley's anemia): Marked anemia, peripheral erythroblastosis, splenomegaly, and skeletal anomalies. Death usually occurs in childhood.
2) Thalassemia minor (Rietti-Greppi-Micheli disease): Hypochromic anemia with slight jaundice, mild splenic enlargement, poikilocytosis, microcytosis, and increased resistance to hypotonic saline solutions; erythroblasts are not present.

Singer and others have subdivided thalassemia into five groups: (1) thalassemia major, (2) thalassemia intermedia, with less severe but still marked anemia, (3) thalassemia minor, with mild anemia, (4) microcytic erythrocytosis and (5) thalassemia minima with slight leptocytosis only.

HEREDITY

The genealogical studies of Neel and Valentine in 1945, demonstrated that the erythrocyte abnormality in this disease is inherited through a pathological gene transmitted from the father or mother. Children carrying one pathological gene (heterozygous) are minimally affected, whereas children receiving the pathological gene from each parent (homozygous) are severely affected. It is therefore thought that the homozygous state of this disease is thalassemia major (Mediterranean anemia, Cooley's anemia) and the heterozygous state, thalassemia minor, (Rietti-Greppi-Micheli disease). Families may have two, three or even five siblings affected with the homozygous severe form; parents of these children frequently have the symptomatic heterozygous disease.

Thalassemia major is a rather common disease in the Mediterranean countries. In the pediatric hematology clinic at the University of Athens, there is an average of one or two new diagnosed cases per month. Neel and Valentine, in Italy in 1945, reported one case of thalassemia major for each 2,368 births; they reported the heterozygous state to exist in one out of each 25 persons.

SYMPTOMATOLOGY

Thalassemia Major (Mediterranean Anemia, Cooley's Anemia)

The affected child is usually described as normal at birth and remains well during the first months of life. Although the age at the onset of the disease is difficult to determine, symptoms seldom arise during the first year. Pallor is usually the first evidence of the disease; anorexia is common.

When the condition is fully developed, the clinical picture is characteristic. The skin is a pale muddy color. The child appears small for its age and the head is disproportionately large. Mongoloid facies is characteristic of the well advanced disease; only a few patients escape this appearance. This abnormal facial configuration is the result of a maldevelopment of the orbital and malar bones which causes some prominence of the eyes with epicanthal folds and a suggestion of a slant. The cheek bones are prominent. The bridge of the nose may be sunken and the eyelids puffy.

Cardiac enlargement is often found, and in advanced stages, edema and effusions into the serous cavities are present. Ecchymotic lesions due to a bleeding tendency sometime develop. There may be moderate lymphadenopathy but this is never striking, whereas enlargement of liver and spleen is always a prominent feature. Splenomegaly is earliest to appear and often extreme; the spleen feels quite hard to palpation. The liver may also reach a great size, and is firm and smooth to palpation. Chronic leg ulcers, like those seen in sickle cell anemia, are rare. Symptoms of anemia usually increase steadily in severity although some patients have stationary periods during which they are relatively comfortable.

The anemia itself is microcytic and hypochromic and has the following characteristics:

1) Red blood cell count is often between 900,000 and 3,000,000 per cu. mm. Hemoglobin usually ranges between 5 and 8 Gm. per 100 ml.
2) The presence of large numbers of nucleated red cells is typical, there frequently being 100 to 200 nucleated red cells per 100 white cells. The majority of nucleated red cells are typical normoblasts and microblasts in immature stages.
3) The red cells have a significant morphological anomaly. Present are:
   A) Microcytosis, poikilocytosis, anisocytosis.
   B) Target cells, which vary greatly in size, contain little pigment and may be distorted in shape and unusual in appearance, so that it is easy to accept them as being formed exclusively by a thin colorless membrane. Pigment within these cells outlines the periphery. In the center of the cell there is an additional circular area of pigment, and usually bridges of pigment joining the central and peripheral zones. The target cell may also be found in other hemolytic anemias.
   C) Fragmentocytes which are, properly speaking, portions of red cells which are believed to result from splenic action.
   D) Howell-Jolly bodies and stippled erythrocytes which are common but are not confined to cases of thalassemia alone. Reticulocytosis is usually marked.

4) There is increased resistance to hypotonic saline solutions. Erythrocytes in this disease are able to absorb more fluid without lysis than are normal red cells.
5) There is also decreased mechanical fragility of the deformed erythrocytes.
6) The hemoglobin in this disease is resistant to alkali denaturation and is therefore thought to be fetal hemoglobin. More than 50 per cent of hemoglobin in patients with thalassemia major is of the alkali-resistant variety.
7) The leukocyte count is usually increased, ranging between 10,000 and 50,000 per cu. mm. There may be myeloid stimulation with the appearance of myeloblasts and myelocytes.
8) The platelet count is usually normal.
9) The icterus index is elevated and the indirect van den Bergh reaction is positive.
10) The plasma copper and serum iron are above normal, according to Huguly, Ashenbrucker and Wintrobe.
11) There is usually a moderate increase in urobilinogen in both stools and urine. There is increased fecal excretion of coproporphyrin.

Roentgenographically, there is widening of the diploic spaces of the skull; both outer and inner tables are thin. The appearance of the skull frequently suggests hair standing on end. These roentgenographic changes in the skull do not always parallel the changes in the remainder of the skeleton or the severity of the anemia; some patients show no significant skull abnormalities. In the long bones of the extremities, the medullary portion is widened and the cortex thinned. The bones of the hands and feet are typically rectangular in contour; the medulla is trabeculated and gives these bones a mosaic pattern.

Bony abnormalities have been observed as early as the fourth and fifth month of life. The earliest lesions in the skull occur usually in the frontal bones. In the long bones, the most striking findings are usually found in the distal ends of the femora. Lesions in the bones of the extremities regress with age, while those of the skull, spine, and pelvis persist and increase. Spontaneous fractures, however, are unusual.

Thalassemia Minor (Rietti-Greppi-Micheli Disease)

Cases of this heterozygous state are usually discovered by chance in adolescents and adults during routine blood examination for a mild anemia. Hypochromic anemia, microcytosis, poikilocytosis, increased resistance to hypotonic saline solution, the presence of the trait in other members of the family, and alkali-resistant hemoglobin, are characteristic. Nucleated red blood cells are absent; target cells are usually present but not in large numbers. There may be moderate enlargement of the liver and spleen. Erythrocytes from patients with thalassemia minor when transfused into a healthy individual have a normal life span while the survival time of cells from subjects with thalassemia major is shortened.

DIAGNOSIS

The diagnosis of thalassemia major offers difficulties only in the early stages. In the well developed stage the condition is rarely missed. The following findings are significant:

Incidence: Even though the disease is seen in many parts of the world, the patient is usually descended from peoples living on the shores of the Mediterranean Sea.

Appearance: Mongoloid facies (usually not an early feature).

Physical examination: Signs of severe anemia, cardiac enlargement, spleen enlarged and firm, liver less so.

Blood: Severe microcytic hypochromic anemia, erythroblastosis, polychromatophilia, red cell stippling, target cells, excessive red cell fragmentation, reticulocytosis and leukocytosis; increased resistance to hemolysis in hypotonic saline, alkali resistant hemoglobin.

Roentgenographic findings: As previously described. During infancy skeletal changes similar to those present in thalassemia major may be noted in Gaucher's disease or in other proliferative reticulosis.

Thalassemia minor is usually recognized by the typical blood morphology occurring in an asymptomatic or mildly anemic adolescent or young adult. Erythroblasts and bone lesions are usually absent, and hepatosplenomegaly is usually mild. Occasionally individuals with thalassemia minor may have a severe anemia and clinical manifestations. The physician may be called upon to give an opinion as to whether a given person is a carrier of the disease. The decision is frequently difficult since there are only certain hematologic findings present in the heterozygous state; these may sometimes be absent, and contrariwise may appear in other anemias.

Target cells, while a prominent finding in thalassemia, are not exclusively confined to this condition. The striking resistance to hypotonic saline solutions, while again not confined to patients with thalassemia, is useful in diagnosis. There are, however, certain patients with the heterozygous state in whom the resistance to hypotonic saline solutions is normal.

Mooney, in 1952, examined relatives of patients in Malta suffering from Mediterranean anemia, and considered a combination of increased resistance to hypotonic saline solution and stippling of erythrocytes as the most definite criterion for diagnosis of existence of the trait. Such a combination was absent in only one case he studied, and was never present in anemias of other etiology. Mooney mentioned nothing about the presence of alkali resistant hemoglobin as being an aid in discovering the heterozygous state.

It has become apparent during the last few years, however, that a certain increased percentage of alkali resistant hemoglobin is to be found in all forms of anemia. Therefore, for an increased amount of alkali resistant hemoglobin present in the blood to be of aid in discovering cases of thalassemia minor, the upper limit of normal value for percentage of fetal hemoglobin must first be determined for each age group.

COURSE AND PROGNOSIS

Thalassemia minor is usually compatible with a normal life span. Difficulty seldom arises. Unlike, however, the other chronic hemolytic anemias with which it may be superficially confused (sickle cell anemia, congenital hemolytic anemia), the course of thalassemia major is characterized by the occurrence of more frequent and progressively more severe hemolytic crises. Death frequently results from intercurrent infection or thrombotic complications. The earlier in life the disease appears, the more violent the course; when symptoms appear during the first year, children often die within six months of the diagnosis. When symptoms appear later, death may be delayed for some years.

PATHOGENESIS

Thalassemia major is considered to be a genetically transmitted primary abnormality of erythropoiesis. Astaldi and Tolentino, in 1952, examined bone marrow specimens from persons suffering from this disease and observed various abnormalities, the chief of which was an increased time of formation of the normal erythrocyte. Early forms in the erythrocytic series show a red fluorescence and contain glucopolysaccharide or mucopolysaccharide in the cytoplasm. The presence of a high serum iron in spite of hypochromia of the red cells suggests that there may be a faulty utilization of iron in the elaboration of hemoglobin. In recent studies, it is believed that the metabolic defect is in the pyrole synthesis.

Electrophoretic studies have shown that a large but variable proportion of hemoglobin (40 to 90 per cent) in thalassemia major is of the fetal type. Two peaks may be seen, one representing fetal hemoglobin, the other, adult hemoglobin. In thalassemia minor only the normal adult peak is observed. The results of measurement of alkali resistant hemoglobin are similar. It is unknown if the alkali resistant hemoglobin present in thalassemia major is identical with fetal hemoglobin or some other pathological hemoglobin with some characteristic attributes of fetal hemoglobin. The recent experiments of Chernoff strengthen the opinion that the alkali resistant hemoglobin of thalassemia is identical with fetal hemoglobin. The issue, however, remains unsolved, whether the initial abnormality in thalassemia major is an abnormality of red blood cell formation, or a molecular abnormality of hemoglobin, or both. The erythroblastosis and the increased erythropoiesis seen in this disease are results of increased destruction of abnormal red cells. Proof of this is offered by thalassemia minor in which destruction of erythrocytes is not marked; the bone marrow can compensate for this mild hemolysis by only a moderate increase in erythroblastosis. Little or no anemia results, and erythroblastosis is absent.

COMBINATION WITH OTHER ABNORMAL HEMOGLOBINS

Various combinations of the thalassemia trait with one or more of the other abnormal hemoglobins have been described. The most common combination results in sickle cell-thalassemia disease. In these cases, the clinical picture resembles that of sickle cell anemia. Other reports have described hemoglobin C-thalassemia in Negroes, hemoglobin E-thalassemia in Thailand, and in one American family of Italian, Spanish, Hindu and Guatamalan origin. A combination of sickle cell-thalassemia-hemoglobin C has also been reported.

THERAPY

Copper, arsenic, oral or intravenous iron, vitamin B_{12}, liver extract, splenic, pancreatic, and adrenal extract, cortisone, and roentgen therapy have all been tried in the therapy of thalassemia major and have been found to be without value.

Repeated blood transfusions are the mainstays in prolongation of life in these patients. Splenectomy may be of value in selected cases when it is desirable to prolong the survival of transfused erythrocytes. Under such circumstances, transfusion requirements may be reduced by 25 to 50 per cent. If splenectomy is to be performed, it should be delayed until later childhood due to the recently reported probably increased susceptibility to fatal infections of young children following splenectomy. In addition, analysis of splenic tissue in many cases has shown substantial deposits of iron, so that it is possible that premature removal of the spleen can divert additional amounts of iron to other parenchymatous organs with resultant interference with function.

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CYSTIC DISEASE OF THE LUNGS

George William Ware, M.D.*

When chest roentgenograms taken in young infants who manifest definite evidence of respiratory difficulty, with or without superimposed infection, are reported as demonstrating cyst formation in the lung (with or without fluid or an associated pneumonic process), three entities should come to mind. These, I think should be kept separate even though, since Dr. Caffey first reported his work, there is often a blending of one group into the other in the minds of pediatricians.

The first of these entities is what is spoken of as congenital cystic disease of the lung. Many cases of cystic disease were falsely labelled this in the past, and many cases were undoubtedly operated on that need not have been if one had used tincture of time and allowed them to resolve.

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From a discussion at weekly Friday conference.

Congenital cystic disease of the lung still exists, and I do not think we ought to go completely overboard and fail to recognize that it can, and actually does, occur. Congenital cystic disease of the lung may manifest itself at any age, and may be discovered either during routine roentgenographic survey or during investigation of superimposed infection.

The second category I choose to call post-pneumonia pneumatocele in an attempt to get away from the word "cyst." This entity, of course, is seen following pulmonary infection. The third category I call lobar emphysema. An infant with this condition may present a picture of marked respiratory distress and have an x-ray picture which looks roughly like a pneumothorax.

Concerning etiology of these three conditions, congenital cystic disease of the lung is truly congenital. It is most probably due to bronchial dilatation, or separation of bronchial buds from the bronchi early in embryonic life. These cysts may or may not be connected with the tracheobronchial tree. Depending on whether they are connected, they may or may not contain air; they may be filled with fluid or contain no fluid whatsoever. Classically, the congenital cyst should be lined with the ciliated columnar epithelium seen in the remainder of the bronchial tree and should contain smooth muscle and cartilage in its wall. If all of these are present, one could theoretically distinguish congenital cystic disease from all the other entities which we shall discuss. If, however, infection supervenes, this may not hold true.

The etiology of the post-pneumonia pneumatocele is somewhat of a problem. It becomes much easier to understand if this condition is thought of merely as a form of obstructive emphysema. A bronchiole becomes plugged with infectious material only to the extent that air may pass on the way into the alveolus but is unable to get out, the so-called "ball-valve" mechanism. The cysts, then, are slowly enlarging alveoli. Another factor involves the pathology of the pneumonic process itself. There is frequently a peri-bronchial infection which may proceed to abscess formation. This abscess then ruptures into the bronchus allowing a patent connection between bronchus and peri-bronchial abscess. This abscess will also enlarge with air entering and not completely escaping. As long as this check-valve mechanism persists, the cyst will persist and fluctuate in size. Staphylococcic pneumonia is probably the most common predisposing cause, mainly because we are seeing more of it these days, but of course, streptococcal, pneumococcal and Friedlander's pneumonia all may initiate the chain of events.

Lobar emphysema has a mechanical basis in most instances. These infants usually develop an enormous amount of emphysema of one lung, and with the over-distension of a lobe of that lung frequently come to surgery. At operation a mechanical factor is found giving rise to blocking of a bronchus. In certain instances there has been an abnormal blood vessel, in others there is chondromalacia of the cartilaginous rings of the bronchi. Sometimes there is an excess flap of mucous membrane which actually acts as a flap which closes on expiration. In some infants, no actual cause can be demonstrated either at surgery or in the pathology laboratory.

DURATION

Congenital cystic disease will of course persist indefinitely. Congenital pulmonary cysts have been demonstrated in persons dying at age 70. The post-pneumonia pneumatocele may persist for days, weeks, or even years. It usually appears for the first time, however, during the convalescent stage of the pneumonia. The pediatrician is just congratulating himself that his patient is getting well when on a routine x-ray, fluid-filled cysts which cannot be differentiated from abscess are demonstrated. Even though these may fluctuate in size and look pretty threatening, the child is usually clinically well. Lobar emphysema will progress for days and weeks, and unless treated may well terminate fatally.

X-RAY

X-ray of the chest may be of some value in differentiating these conditions but is certainly not diagnostic. In general, we may say that in congenital pulmonary cystic disease (fig. 1), the cyst wall is usually thicker than that which is seen in the post-pneumonic pneumatocele (fig. 2). Fluid may or may not be present. There is, however, a constant size to the cyst and this is important. The pneumatocele, even though it may look perfectly like an abscess cavity (fig. 3), has an extremely thin wall; it may or may not contain fluid. More important, its size will vary greatly. An x-ray taken at eight o'clock in the morning may demonstrate a huge cyst while one taken at two o'clock in the afternoon may show a great decrease in size. It depends wholly on how much air is actually in the pneumatocele at the time the film is taken. In cases of lobar emphysema, the usual x-ray report is tension pneumothorax. This pneumothorax is frequently progressive and no fluid is described.

ROLE OF INFECTION

The time element of infection, if present, is important. In congenital cystic disease the x-ray picture is present before infection occurs while post-pneumonia pneumatoceles, with or without fluid, appear only *after* infection. Consequently, any prior chest films may well be absolutely diagnostic. Lobar emphysema bears no relation to infection. Sometimes the infant who is recovering from pneumonia and develops post-pneumonia

FIG. 1. X-ray of chest in AP view shows a circumscribed, radiolucent lesion in the 2nd and 3rd interspaces anteriorly on the left. The periphery of this lesion is surrounded by a zone of fibrosis. This represented a congenital lung cyst.

pneumatoceles may contract secondary infection of these cystic lesions. A secondary rise in temperature and the appearance of fluid in these lesions may give a clue to this complication. Secondary infection of the pneumatocele is, however, uncommon.

THERAPY

How do we treat these lesions? In the case of the post-pneumonia pneumatocele, the tendency with the onset of their appearance is to relax since we know that they will go away by themselves. Certainly in ninety per cent of cases this is true. However, it must be realized that two complications may well occur. These are 1) rupture with formation of a tension

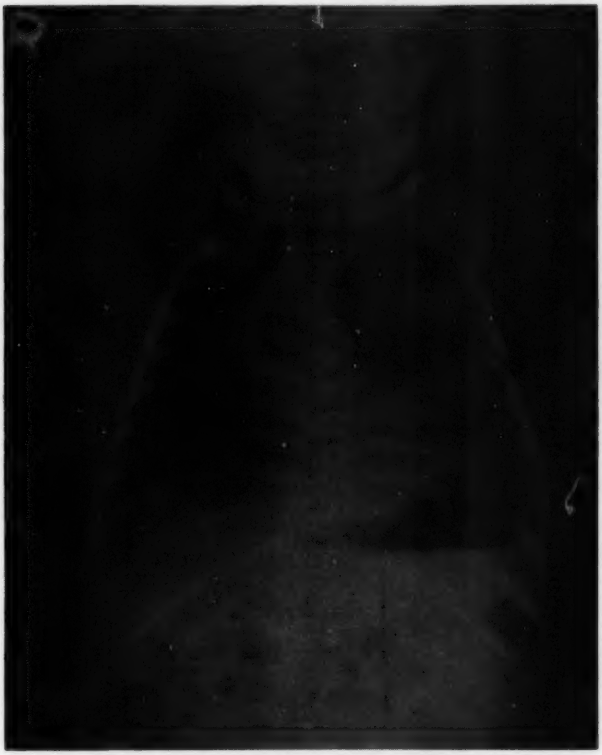

FIG. 2. X-ray of chest in AP view shows a shift of the upper mediastinum to the right. The upper portion of the left chest is filled with an emphysematous bleb which extends into the mediastinum. This represents a regional obstructive emphysema following a staphylococcic pneumonia.

pneumothorax, and 2) rupture into the pleural space with development of emphysema. The most common time for these complications to occur is in the earliest phase of "cystic" development when these cystic areas first begin to appear in the x-ray. The second most common time is when they become filled with fluid where previously they had been empty. A rise in temperature usually appears at this time.

In general, with the post-pneumonia pneumatocele, the treatment is conservative. If, however, respiratory embarrassment becomes extremely severe, aspiration should be considered, but aspiration itself may actually result in a tension pneumothorax. If aspiration is only of temporary help,

FIG. 3. X-ray of the chest in the AP view shows a large, circumscribed lesion in the lower half of the left lung with a fluid level in its upper portion. This represents a lung abscess.

one can do what is called a Monaldi-type drainage. An incision is made under local anesthesia over the cystic area and some type of irritating pack is placed adjacent to the pleura to seal the pleural surfaces. Two days later when the cyst wall is plastered to the parietal pleura, a re-operation is performed, the cyst incised, and a water seal drainage instituted. Some of the pneumatoceles have been resected. I do not think that this has been done since 1942, and it certainly is not recommended.

The treatment of congenital cystic disease is certainly not aspiration since when one attempts to aspirate, he is passing a needle through normal lung tissue and again, tension pneumothorax may develop. If, however, congenital cystic disease of the lung gives rise to symptoms, surgical removal of the cyst is the only known form of therapy.

Cases of lobar emphysema have been operated on. It is difficult to say what is the exact and proper treatment at the present time but aspiration should probably be tried first. Tension pneumothorax has been known to occur, however, and one should consider whether or not surgery should be done since lobar emphysema is a rather rapidly progressing condition.

PURPURA IN CHILDHOOD

Jack J. Rheingold, M.D.,* Sanford Leikin, M.D.†

Two common causes of purpura in childhood are discussed and recent advances in diagnosis and treatment emphasized.

CASE 1

Idiopathic Thrombocytopenic Purpura

This 2 year old white boy was admitted to Children's Hospital with a chief complaint of fever and generalized ecchymoses of seven hours duration. He had been in excellent health until one week prior to admission when he passed a blood-streaked stool. On the day of admission a small hematoma was noted to have developed behind the right ear. Seven hours prior to admission a fever developed and rose to 105 degrees. This was accompanied by the passage of two watery stools and the appearance of multiple petechiae and ecchymoses over the entire body.

Past history and family history were non-contributory.

On admission the child appeared to be a well developed, well nourished two year old white boy who was moderately toxic. Rectal temperature was 101.6 degrees. There were numerous petechiae and small ecchymotic lesions over the entire body, marked over the face, neck, and anterior chest. Petechiae were also noted over the tonsils which were erythematous and covered with a follicular exudate. There was moderate nuchal rigidity. No lymphadenopathy or hepatosplenomegaly were present. The remainder of the physical examination was within normal limits.

Initial diagnostic impressions were acute follicular tonsillitis, possible meningococcemia with meningitis, and possible blood dyscrasia of undetermined etiology.

Spinal fluid obtained shortly after admission was completely normal, but the site of lumbar puncture continued to bleed long after the procedure was terminated. A petechial smear revealed no evidence of meningococci. Treatment by vein with penicillin, chloramphenicol, and sulfadiazine was instituted. A large hematoma developed at the site of intravenous infusion.

Urinalysis was normal. Blood culture showed no growth. Initial blood count revealed a hemoglobin of 9.9 Gm. per 100 ml., hematocrit 32 per cent, and white blood count of 7,500 per cu. mm. Less than 10,000 platelets per cu. mm. were present and examination of the peripheral blood smear demonstrated a markedly reduced number of platelets.

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Treatment with prednisolone was then started, in an initial dose of 10 mg. and a maintenance dose of 5 mg. every six hours. Intravenous administration of antibiotics was discontinued, and choramphenicol and sulfadiazine were given orally.

Examination of the bone marrow the day following admission demonstrated the red and white cell series to be normal. The number of megakaryocytes was noted to be somewhat reduced and they did not appear to be producing platelets. The impression of idiopathic thrombocytopenic purpura was confirmed.

Three days after admission, the ecchymotic lesions having almost completely cleared, the child was discharged to receive 20 mg. of prednisolone daily. Platelet count on the day of discharge was 30,000 per cu. mm. One week following discharge his platelet count was 300,000 per cu. mm. and numerous platelet clumps were noted in the peripheral blood smear. He remained asymptomatic and it was planned gradually to reduce prednisolone medication.

DISCUSSION

Dr. Rheingold:

It is my feeling that this child had idiopathic thrombocytopenic purpura, or ITP as it is frequently called. The question must be raised whether the purpura was actually secondary to the moderately severe infection which was present. Against this are the facts that a week prior to this acute infection the child lost an undetermined amount of blood while having a constipated stool, and a day before the onset of infection had an ecchymotic lesion behind his right ear.

ITP is an extremely interesting and, in a sense, a very mysterious disease. We have observed in our practice, three people who have relapsed, 10, 17, and 18 years respectively, following splenectomy for ITP. All were completely asymptomatic in the interim. The occurrence of such cases makes the accumulation of accurate statistics quite difficult.

We have seen another woman who, a number of years ago, at the age of nine or ten had had ITP. Splenectomy was recommended but permission for operation was denied by the father until the onset of the child's menses. Bleeding at that time was so profuse that permission for splenectomy was then given and the operation performed. She was completely "cured" and has since had no difficulty whatsoever. However, a year after her first marriage at 19 years of age, she delivered a child who was born with ITP. The child recovered completely at about two to three months of age. The mother subsequently divorced her first husband, re-married (this rules out the first husband as a possible source of the disease) and later delivered two more children, both of whom were found to have ITP at birth, so whatever antibodies the mother carried she was still able to transmit to her offspring years after her apparent cure following splenectomy.

The etiology of ITP is not known. ITP may represent the initial complaint in adult patients who have lupus erythematosus disseminata later on in life. Some cases of ITP seem to be associated with platelet antibodies; some do not. These antibodies, when present, not only destroy the circulating platelet but apparently affect the megakaryocyte as well. The disease may then be defined as a form of thrombocytopenic purpura which may or may not be associated with platelet antibodies, manifested by a bleeding diathesis together with absence or marked reduction of platelets in the peripheral blood and the presence in the bone marrow of megakaryocytes which are not forming platelets. Physical examination in these patients usually reveals only evidence of bleeding. It is unusual to find a splenomegaly to any degree; if splenomegaly is present, another disease should be considered.

Patients with ITP, either children or adults, may have bleeding from any orifice. There may, however, be bleeding only into the skin. Vaginal bleeding is a common complaint and many women have had dilation and curettage of the uterus multiple times and even a hysterectomy performed for what was later discovered to be ITP. We have preached for many years that if a patient who is bleeding presents himself to a general practitioner or specialist, and the physician is unable or unwilling to perform a complete clotting study, he should at least examine a peripheral blood smear. It is quite simple and requires very little experience to examine the peripheral blood and determine whether the platelets are normal, increased, or reduced in number.

The platelet is an extremely interesting cellular element and probably should be thought of as being very much like a "blotter." Indeed, one of its functions may be, instead of making various substances which help initiate and promote clotting, to absorb these substances by its capacity as a sponge. This laden sponge then migrates to an area where bleeding is taking place and is destroyed, releasing the agents necessary for the clotting mechanism to occur. This absorptive capacity of the platelet occurs not only with substances necessary for clotting, but with other substances, e.g., Dextran®, as well.

The platelet has other important properties necessary for normal cessation of bleeding. It releases serotonin, which in turn causes vasoconstriction; it may also act as a mechanical block to a capillary leak.

What are the positive laboratory findings in the individual who has thrombocytopenic purpura? First is a prolonged bleeding time which is related to a number of factors. The platelets are reduced in number, so fewer are available to plug up the damaged capillaries. The amount of liberated serotonin, which causes vasoconstriction, is reduced. Many times the bleeding time in this disease may be prolonged to 10 to 15 minutes (upper limit of normal: six to seven minutes) and may need to be stopped by mechanical pressure. Second, since normal clot retraction is dependent on an adequate number of platelets, clot retraction is reduced, and a very poor clot retraction occurs. Third, there is an abnormal prothrombin consumption time. This test may be explained as follows: When blood drawn from the vein of a normal individual clots, the amount of thromboplastin present in the serum is adequate to convert the serum prothrombin to thrombin. Therefore, in the normal person, there will be little or no prothrombin remaining in the serum and the prothrombin time will be significantly increased. In the individual who has a quantitative or qualitative platelet defect (as well as the patient with hemophilia who lacks one of the plasma factors), enough thromboplastin is *not* formed. Consequently, prothrombin, although present in normal amounts, is not completely utilized to form thrombin. The serum consequently still contains a large amount of prothrombin and a prothrombin time performed on such a serum is not distinctly altered from normal.

Examination of the bone marrow is very necessary in an individual suspected of having thrombocytopenic purpura. It is not always possible to differentiate these patients, by examination of the peripheral blood alone, from those with leukemia or with damaged bone marrow as a result of some unknown toxin.

How should the patient with idiopathic thrombocytopenic purpura be treated? Fortunately, ITP in the child is a relatively benign, self limited disease. Over a period of time the platelet count will gradually return to normal. It is practically never necessary to perform a splenectomy on a child with ITP. If the child continues to have difficulty with bleeding, we would prefer first to treat him with steroid medication, for example, prednisone or prednisolone, in a dose of 20 to 40 mg. per day, depending on the size of the child. If the steroids do nothing else, they apparently improve the capillary stability, so that these children, even though their platelet counts continue to remain low, have no further bleeding.

How long should one wait before removing the spleen in the child who is continuing to bleed? I am extremely conservative in this regard. In dealing with a child, in whom the danger of cerebral vascular hemorrhage is small, I would be inclined to wait as long as possible, since I have never seen a child whose platelet count did not eventually rise to normal and whose bleeding then stopped. In the teen-age group, it is a different story; the adolescent should probably be considered as an adult as far as his reaction to ITP is concerned. There is an ever present danger of cerebrovascular accident in these individuals. The adolescent will, however, almost universally respond to steroid medication. In adults, splenectomy is probably the most important method of treatment.

There have been a number of reports in the recent medical literature concerning the occurrence of moderately severe to severe infections following splenectomy in children. This has added to everyone's concern about performing splenectomies unless absolutely necessary. Consequently criteria for performing splenectomy in ITP should be well defined.

CASE 2

Allergic Purpura

This 3 year old white girl was admitted to Children's Hospital on September 5, 1957 with the chief complaints of swelling and easy bruising of both feet. She had been well until six days prior to admission when she complained of pain in her right foot. Hemorrhagic lesions on both feet and swelling of both ankles were noted by her parents at that time. Her private physician was called and admitted her to another hospital where a bleeding time, clotting time and platelet count were performed and reported as being normal. After a five day hospital course marked by persistence of skin lesions and ankle swelling, she was transferred to Children's Hospital for further evaluation.

The child's past history revealed that seven weeks prior to admission she had had "a sore throat and swollen tonsils" for which she was treated with penicillin. There was no familial history of a bleeding tendency.

On admission to the hospital the child appeared to be well developed and well nourished, and in no distress. She was afebrile. General physical examination was completely normal except for both lower extremities which were covered by patchy areas of discoloration and scattered petechiae. There were small macular lesions and scattered ecchymotic areas present on both buttocks. The joints appeared normal.

Initial laboratory results included a blood hemoglobin of 10.5 Gm. per 100 ml., hematocrit 34 per cent, and a white blood count of 13,040 with a normal differential. Platelets in the peripheral blood smear were adequate. Her urine was hazy in appearance, had a specific gravity of 1.032 and contained 25 to 35 white blood cells and 30 to 40 red blood cells per high power field. Bleeding time, clotting time, and prothrombin time were all well within normal limits.

During her hospital stay the patient began passing gross blood in her urine and melena developed. Her blood hematocrit fell to 25 per cent and she was given a transfusion of 150 ml. of whole blood. Melena continued, however, and was accompanied by vomiting, the vomitus containing occult blood. Four days after admission additional purpuric lesions appeared on her right foot and both buttocks. Because of bacilluria and pyuria with sensitive organisms, tetracycline therapy was started. Six days following admission additional purpuric lesions appeared on her buttocks and legs but her general condition was much improved. An antistreptolysin O titer at the time was reported as 2,500 units.

On the tenth hospital day therapy with penicillin intramuscularly and prednisone orally were initiated. No new purpuric lesions appeared, the purpuric lesions already present rapidly disappeared and she was discharged to the care of her private physician, asymptomatic, on the fourteenth hospital day. Prednisone therapy was maintained but was gradually being reduced.

DISCUSSION

Dr. Leikin:

Allergic purpura is a typical non-thrombocytopenic purpura associated with some common symptoms of allergy, such as erythema, urticaria, and submucous or visceral effusions. When this symptom complex is associated with either gastrointestinal or joint symptoms it is also known as Henoch-Schönlein purpura. This, of course, is a disease of the blood *vessel.* As far as it is known, there is no abnormality of any cellular or humoral component of the blood. The bleeding tendency is due to an increased permeability of the capillary endothelium which permits the passage of plasma and blood cells into the extra-vascular space. Several workers who have performed tissue biopsies have found cellular infiltration and inflammation in the perivascular tissue. Because of these findings this disease is thought to fall into the group of collagenous disorders, and to be a hyperimmune disease, antibodies being produced against capillary endothelium. When an exciting cause can be found, some particular food or a bacterial infection has usually been incriminated. The most common etiological bacterial organism is the streptococcus, and it is not unusual to find a history in these patients of a sore throat several days to several weeks before the onset of purpura. At other times the purpura appears during the height of a streptococcal infection. Investigators from Israel have recently reported a high percentage of patients with allergic purpura who were either in the convalescent stage of a streptococcal pharyngitis or had a high blood titer of antistreptolysin O.

Other evidence which suggests that allergic purpura should be placed in the group of collagenous disease is the frequent presence of complicating nephritis. This has been reported in up to 47 per cent of patients with allergic purpura. In these cases evidence of nephritis appeared during the course of the purpura or very shortly thereafter.

The disease initially presents clinically with purpura and joint swelling. The purpura is most commonly found on the extremities (usually the lower extremities). The body is usually spared. Another common site is the buttocks. The lesions are somewhat different from those seen in thrombocytopenic purpura. They are frequently rather diffuse, are not elevated, quickly fade to a bluish color, and disappear quite rapidly, whereas the thrombocytopenic purpuras usually go through all stages of hemoglobin breakdown. I have made it a rule never to diagnose allergic purpura unless erythema as well as purpura is present.

Bloody effusions are frequently present. These effusions not only occur into the joints but into the mucosa of the intestine, leading to the high incidence of gastrointestinal bleeding. Necrotizing lesions advancing to gangrene of the digits are not rare, and frequently cause confusion in the differential diagnosis of this condition from meningococcemia.

The hemorrhage seen in these patients is usually not severe, and most, fortunately, do not require blood transfusions. There is usually only a small amount of blood streaking of the stool or bleeding from the nose, and other forms of gross hemorrhage are not common.

Gastrointestinal symptoms are very prominent and may appear before the onset of purpura. Intussusception has occurred from a bloody effusion serving as an intussuscipiens, and frequently it is difficult to determine whether intussusception is present alone or combined with allergic purpura. Joint involvement may raise the question of rheumatic fever, especially since pericarditis has been reported in this disease. Microscopic hematuria is common, and evidence of renal damage including hypertension may remain after the purpura has terminated. For this reason, it is important that these patients be followed most carefully for continuing evidence of nephritis.

Since allergic purpura is a disease of the blood vessels, all tests of blood coagulation are normal. The only abnormality which may be found is an increased capillary fragility but even this is not universally present. The course of allergic purpura, in childhood at least, is usually self limited. Skin and joint abnormalities may last for several weeks but do not recur.

Treatment is essentially symptomatic. When the disease is prolonged however, or when there appears to be danger of serious bleeding, steroid medication should probably be considered. The rationale of adrenal steroid therapy would be to increase vascular integrity and possibly reduce antibody production, even though no one has yet been able to demonstrate any specific antibody formation in allergic purpura. Flavinoid drugs have also been recommended but are probably of little, if any, value.

EDITORIAL

CHANGE IN STAFF

George J. Cohen, M.D.*

On April 1, 1958, Mrs. Thelma Waller completed three years of service as General Manager of Clinical Proceedings of Children's Hospital. Largely because of her assiduous and untiring work, Clinical Proceedings has shown considerable progress during this time. Quite obvious to all our subscribers is the fact that their copies of the Proceedings are arriving on time. Less apparent, except to the editorial staff, is the vast improvement in the management of the business and clerical details in the Proceedings' office; the emancipation of the Editor-in-Chief and Managing Editors from such responsibilities has allowed them to devote more time and energy to the actual editing of copy with, we hope, better quality material appearing in the Proceedings.

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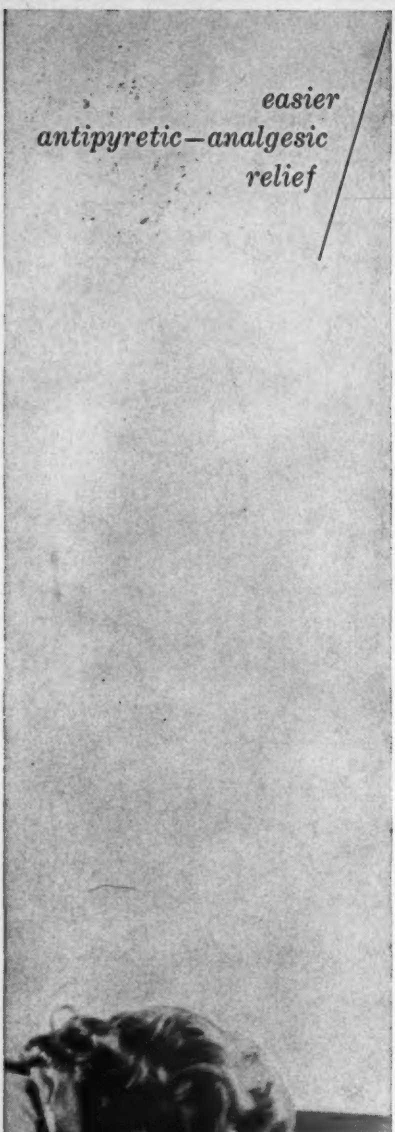
* Junior Associate Staff, Children's Hospital.

For personal reasons which cause us to rejoice with her, Mrs. Waller must leave her position with Clinical Proceedings. Her personal gain is our loss, but we publicly thank her for her splendid handling of a difficult job.

At this time, Clinical Proceedings is fortunate to receive a special grant to enable adopting a different organization of its office. We are delighted to welcome as Executive Editor, Gordon Loud, A.B., M.Arch., who comes with a background of scientific study, writing and editing and a keen interest in maintaining and improving the status of the Proceedings. Assisting him as General Manager is Robert V. Morin, B.S.F.S.

We are most fortunate in having these capable gentlemen in our office and look forward, with them, to a bright future for Clinical Proceedings of Children's Hospital.



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